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LDL cholesterol – How low to go?

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Abstract

Epidemiology and the results of large-scale outcome trials indicate that the association of LDL with atherosclerotic cardiovascular disease is causal, and continuous not only across levels seen in the general population but also down to sub-physiological values. There is no scientific basis, therefore, to set a target or 'floor' for LDL cholesterol lowering, and this presents a clinical and conceptual dilemma for prescribers, patients and payers. With the advent of powerful agents such as proprotein convertase/subtilisin kexin type 9 (PCSK9) inhibitors, LDL cholesterol can be lowered profoundly but health economic constraints mandate that this therapeutic approach needs to be selective. Based on the need to maximise the absolute risk reduction when prescribing combination lipid-lowering therapy, it is appropriate to prioritise patients with the highest risk (aggressive, established CVD) who will obtain the highest benefit, that is, those with elevated LDL cholesterol on optimized statin therapy.

Introduction

Few topics currently provoke as much heated debate - both in the scientific literature and lay press – as the use of cholesterol lowering therapies to prevent cardiovascular disease (CVD). Reviews, editorials and guidelines provide enthusiastic endorsement of ever more aggressive goals for therapy (1-4), or caution lest there is a drive to overtreatment with insufficient attention paid to risk of side effects and tolerability (5,6), and, of course, cost-effectiveness (7,8). In the pre-statin era, this was not an issue since medications had limited efficacy. Following the unequivocal trial evidence that LDL cholesterol (LDLc) lowering with statins was beneficial in both primary and secondary prevention (3,4,9), there was widespread acceptance of this treatment approach but concerns raised over tolerability especially in primary prevention (6,10), and the medicalization of what was seen, at least in asymptomatic individuals, as a lifestyle issue. It is the demonstration of the success of combined lipid lowering treatments with ezetimibe (11) and, particularly, proprotein convertase/subtilisin kexin 9 (PCSK9) inhibitors (12) that has sharpened the debate since it is now possible to achieve previously unheralded LDLc levels, well below the recommended targets of 70 to 100 mg/dl advocated for example in Europe (4). How low do you go? What are the benefit: risk and benefit: cost/opportunity ratios? Which patients should be prioritised for intensive LDLc lowering treatment? The following discussion sets out the conceptual framework for optimised LDLc lowering, summarizes the clinical trial evidence for combined lipid lowering therapy, and offers therapeutic strategies that may aid in the appropriate use of newly marketed and emerging drugs such as PCSK9 inhibitors, cholesteryl ester transfer protein (CETP) inhibitors, and small RNA- or anti-sense oligonucleotide-based therapies (13).

Context and therapeutic rationale for LDL cholesterol lowering.

Underpinning the rationale for ever more aggressive LDLc lowering in the prevention of the first or recurrent major cardiovascular events is our understanding of the relationship between plasma

cholesterol (mainly carried in LDL) and atherosclerosis, the silent disease process that leads to clinical manifestations of MI and ischemic stroke. Cholesterol is one of the major risk factors alongside raised blood pressure, smoking, and diabetes. Consideration of the totality of the evidence has led an international expert panel to conclude that LDL is a (the?) major causal agent in the pathogenesis of the disease (14) and differs conceptually from others such as smoking and high blood pressure which can be viewed as aggravating factors that accelerate plaque progression once lesion formation is initiated. Evidence to support this view comes from epidemiological investigations where populations with lifelong low cholesterol levels have virtually no CVD despite having an elevated inflammatory state (14, 15). Likewise, experiments of nature – inherited conditions of low and high LDLc - reveal reduced or elevated incidence of CVD independent of the presence or absence of other risk factors. Homozygotes for PCSK9 loss-of-function mutations have substantially lower lifetime LDLc levels and a much-reduced risk for CVD (16), while individuals with familial hypercholesterolemia (FH) have raised LDLc from birth and, if untreated, suffer a MI typically in mid-life if heterozygous, and in childhood if homozygotes (17,18). Should we therefore consider LDLc as a risk factor that is best minimised (perhaps not to zero) in analogy with the promotion of smoking abstinence, rather than a physiological parameter that needs to be maintained in an optimal range, like blood pressure or blood glucose?

Figure 1 provides a conceptual framework in which we can understand the impact of LDL on atherosclerosis, the opportunities for intervention at various stages of the disease, and the rationale for profound cholesterol lowering. In considering the potential consequences of reducing LDLc substantially, it should be borne in mind that as children we had a low LDLc; the mean was about 95 mg/dl and the 5th percentile about 65 mg/dl (19). These levels, analogous to those in primates (14), saw us through the developmental challenges of puberty, and a pharmacological return to such values should not of itself be problematic. LDLc rises substantially in men from late teens to mid-life (Figure 1) (19), probably due to a reduction in the activity of LDL receptors with ageing (20). It is this

change in LDLc that likely drives atherogenesis (a similar rise occurs in women after the menopause). Further, an emerging concept, based on the early CVD seen in FH (Figure 1) (14,18), is that what matters most is the integrated length of exposure to elevated levels i.e. accumulated 'LDLc x years'.

Genetic analysis has provided additional insight into the potential effectiveness of LDLc lowering. Mendelian randomisation studies based on moderate-effect variants that alter LDLc levels (14,21,22) have successfully predicted the outcome of clinical trials, and reveal that the benefit of reducing LDLc by a given amount over a lifetime far exceeds that seen when the lipoprotein is decreased using drugs in clinical trials at, on average, about 62 years of age; for example the relative risk reduction for a 39mg/dl lower LDLc from birth is estimated at 54% compared to the 22% seen from meta-regression of statin treatment trials of 5 years duration (21). Put another way, in order to achieve a 50% risk reduction LDLc needs to be decreased by about 35mg/dl if treatment is initiated in early adulthood but by 100mg/dl if started late in life (Figure 1). This differential may be explained by the changing nature of the lesions with age. Resolution of early plaque/ fatty streaks may be more easily achieved with moderate LDLc lowering while much more aggressive treatment is needed to stabilise and regress mature, vulnerable lesions seen later in life.

Clinical trial evidence for the benefits of profound LDL cholesterol lowering.

The first landmark LDLc lowering trials in secondary prevention (4S with 20-40mg simvastatin; (23)) and primary prevention (WOSCOPS with 40mg pravastatin; (24)) used what is now considered 'moderate intensity' statin therapy that reduced CVD risk by about one-third. The benefit of higher statin doses was subsequently examined in a series of studies, most notably PROVE-IT (25) and Treat-To-New-Targets (TNT (26)) and this led to the recommendation that 'high intensity' treatment be used in high-risk individuals with established CVD (3,4). Figure 2A (adapted from (14)) summarises the outcome of clinical trials of LDLc lowering in primary and secondary prevention

settings. It can be seen that there is a convincing continuous relationship between achieved LDLc level in the two arms of a study (placebo vs active drug, or higher vs lower statin dose) and risk of a major coronary event. In European and Canadian guidelines, this evidence base was interpreted to indicate that 'lower is better' and more aggressive LDLc targets were promulgated for high risk-primary and secondary prevention (4,27). Controversially in the most recent revision, US guidelines emphasised treating patient groups aligned with those tested in the landmark trials rather than focussing on achievement of goals (3). While this approach has merits, there have been calls for the reinstatement of targets especially with the introduction of effective add-on therapies (28).

Following years of 'negative' trials examining mainly the potential benefits of raising HDL to address the residual risk in patients on optimised statin therapy (29,30), there has been recently notable success in demonstrating incremental risk reduction from further LDLc lowering using combination therapy with a cholesterol absorption inhibitor (ezetimibe), or a PCSK9 inhibitor (such as evolocumab). IMPROVE-IT was the first of the successful combined lipid lowering trials to report (11). It showed that in well-treated subjects on statin therapy, addition of ezetimibe led to a further decrement in LDLc – from a mean of 74mg/dl to 63mg/dl (with 38% achieving LDL cholesterol levels < 50 mg/dl (31)) – and a decrease in CVD risk of 6.4% ($P=0.016$). This was the first demonstration that a non-statin drug could reduce risk significantly and so reinforced the causal association of LDL with CHD (14) that had been questioned on the basis of the repeated observation that only statins appeared to be able to decrease risk (32). There were no safety signals of concern in the trial comparing the two treatment arms (11), and when all subjects were grouped together and LDLc across the range of <30 to >70 mg/dl related to a range of emergent adverse events over the trial period, there were again no signals that very low LDLc was linked to a higher frequency of adverse events (31). The investigators paid particular attention to non-cardiovascular death, haemorrhagic stroke, and neurocognitive events, all of which had been raised as potential issues. An association of cancer with lower cholesterol was observed but this can be attributed to the inclusion of the placebo

group and the known relationship in the general population that is understood not to be cause and effect (i.e. people with cancer develop low cholesterol levels rather than vice versa). This analysis in very low LDLc subjects mirrors the more comprehensive evaluation that was generated using meta-analysis of lipid-lowering trials (33).

The eagerly awaited FOURIER trial (12) was the first large-scale test of the ability of PCSK9 inhibitors to reduce CVD risk. Change in LDLc was dramatic, from a mean of 92mg/dl to 30mg/dl; patients in this trial had the lowest levels of LDLc yet achieved with pharmacological intervention. Incidence of the primary endpoint was 15% lower ($P<0.001$), and the key secondary endpoint 20% lower, in the PCSK9 inhibitor treated group versus those receiving placebo. As with IMPROVE-IT, the clinical benefit was seen on a background of statin therapy (69.5% were on 'high' and 30.2% on 'moderate' intensity statin regimes). The trial has been criticised due to its short duration and lack of demonstration of an effect on cardiovascular mortality (likely linked features) but over the mean 2.2 years of follow up there were no treatment-emergent safety signals. A concern about neuro-cognitive side effects that had arisen from phase 3 trials of PCSK9 inhibitors (34,35) was addressed in the EBBINGHAUS sub-study (36) where a battery of cognitive assessments was undertaken and the results for subjects on evolocumab found to be essentially identical to those on placebo. The FOURIER investigators embarked on an exploration of the clinical consequences of inducing profoundly low LDLc levels using the whole trial data set in an approach (37) that mirrored that described above for IMPROVE-IT (31). When achieved LDLc for the combined treatment groups was related to risk of cardiovascular endpoints, it was seen that there was no lower limit of efficacy; rather, there was a continuous relationship with a monotonic decrease in incidence of CVD from the group with highest LDLc ($>100\text{mg/dl}$) to that with the lowest ($<20\text{mg/dl}$) (Figure 2B). Even going below 10mg/dl appeared to give further benefit (37). A range of safety concerns was addressed - including liver dysfunction, creatine kinase levels, worsening of diabetes control, cataracts, haemorrhagic stroke, cognition, and cancer – and there was no discernible adverse trend with even

very low LDLc. In a further, detailed analysis of the recognised link between LDLc lowering and increased risk of developing diabetes (38), it was seen in FOURIER that evolocumab therapy on-top of statin over the period of the study did not increase the incidence of type 2 diabetes in the whole cohort or those with pre-diabetes, nor did it appear to worsen glycaemic control in subjects with diabetes at baseline (39). This observation contrasts with findings from Mendelian randomisation studies which showed that having a lower LDLc associated with PCSK9 variants was linked to increased risk of diabetes in a manner similar to that seen for variation in the gene for 3-hydroxy-3-methyl-glutaryl co-enzyme A (mimicking statin therapy) (40). This discordancy between genotypic- and clinical trial – findings reflects the strengths and weaknesses of each approach to determining the benefits and disadvantages on an intervention (see (41) for a review). As noted, the duration of FOURIER at just over 2 years limits the ability to detect late-appearing treatment-emergent side effects, and the genetic observations leave the diabetes link an open question.

The results of IMPROVE-IT and FOURIER, together with the more comprehensive evaluation from meta-regression (33) provide strong evidence that there is no discernible ‘floor’ to the association of LDL with CVD risk, and so far, no safety concern over inducing profoundly low levels of this lipoprotein. The editorial accompanying the FOURIER low LDLc analysis talked of moving from targets to the concept of LDL ‘eradication’ (1).

Pooled findings from phase 3 studies with alirocumab (34, 42) have revealed that, as for evolocumab, in subjects with profoundly lowered LDLc (<15mg/dl and <25mg/dl) there appears to be little of concern regarding safety, although again duration of exposure and the numbers of patients treated render these preliminary conclusions. There was an imbalance in cataract frequency (42) that in theory could have a basis in altered cholesterol metabolism in the eye since cholesterol is an important structural component of the lens (43) and in theory its availability may be

compromised when LDLc levels are very low. This observation needs to be confirmed or refuted in the major ODYSSEY OUTCOMES trial (44).

Of especial importance for both IMPROVE-IT and FOURIER was the finding that the relationship between change in LDLc and reduction in CHD risk fell on the same regression line as that generated by meta-analysis of all the statin based studies (9,11,12,45). The Cholesterol Treatment Trialists Collaboration (CTTC) analysis showed that for each 39mg/dl (1.0mmol/l) lower LDLc there is a 22% decrease in CHD risk over a 5-year exposure to drug therapy (9). Ezetimibe treatment gave an 11mg/dl drop in LDLc and a proportionate 6.5% decrease in risk in the 7-year trial (11). For FOURIER, it is necessary due to the short follow up to take account of the fact that only half the risk reduction is seen in year 1 and correcting for trial length showed that the PCSK9 inhibitor yielded the predicted magnitude of benefit (12,45).

Direct assessment of the extent of atherosclerosis and its relationship to LDLc has been examined in imaging trials where lipid lowering interventions have been shown to slow progression, and induce regression, of atherosclerotic lesions (46). The finding that regression occurs in the majority of patients who achieve very low LDLc levels in the GLAGOV trial of evolocumab treatment (47) reinforces the view that the association of this lipoprotein with the underlying disease process is causal, and further demonstrates that plaque is amenable to considerable remodelling, with resultant beneficial effects on clinical outcomes.

The latest lipid lowering add-on outcome trial to show a significant (but modest) CVD benefit was the HPS-REVEAL study with anacetrapib (48), a drug designed to raise HDL (which it doubles) but that also reduces LDLc by 30% to 40% (48). The trial was powered to see an effect of LDLc lowering in contrast to earlier cholesteryl ester transfer protein (CETP) inhibitor studies that were smaller and of shorter duration (e.g 30). Anacetrapib on top of optimised statin therapy in subjects with already

low LDLc (baseline LDLc was 63mg/dl) gave a 9% risk reduction for a further 29mg/dl decrease in LDLc and a 18mg/dl drop in non-HDL cholesterol and in apolipoprotein B (apoB) (48). This agent has been shown to alter the ratio of cholesterol to protein in lipoprotein particles, which makes accurate measurement of LDLc problematic (49). A better guide to efficacy in these circumstances is likely to be change in apoB, the structural protein in atherogenic lipoproteins (49,50). (Note that the manufacturer has decided not to apply for registration of anacetrapib due to issues associated with the properties of the agent – a particular concern was the substantial accumulation of the drug in adipose tissue (48) - and it is not yet clear if there will be further development of the CETP inhibitor class). A concomitantly reported Mendelian Randomisation ‘trial’ – confirmed the concept that CETP inhibition combined with statin therapy was likely to reduce CVD risk, and again the benefit was predicted to be proportional to the decrease in apoB (LDL particle number) not LDL cholesterol (51), an important finding when considering initiating and monitoring aggressive cholesterol lowering therapy.

There are potential concerns about very low LDLc levels based on observations in the human disorders of abetalipoproteinemia and homozygous hypobetalipoproteinemia (52). Here LDLc and apoB are <30 mg/dl (or zero) and symptoms appear associated with failure to transport fat soluble vitamins and with development of a fatty liver. In this context, it is critical to note that the mechanism of LDLc lowering differs between these deficiency states and the actions of statins, ezetimibe and PCSK9 inhibitors. In abetalipoproteinemia and homozygous hypobetalipoproteinemia, there is defective lipoprotein production in liver and gut (52). Statins by reducing intracellular cholesterol levels induce expression of LDL receptors and so accelerate clearance of LDL from the circulation (14,53), similarly ezetimibe reduces cholesterol absorption and transport to the liver and thereby increases LDL particle clearance (14,53). PCSK9 inhibitors promote clearance of LDL and other apoB-containing lipoproteins from the bloodstream by blocking the action of PCSK9 on LDL

receptors (54). None of the three drug classes appear to alter lipoprotein production rates (14,54), and so transport of fatty substances is likely therefore be preserved with these agents.

Treatment strategies to achieve very low LDL cholesterol.

In light of the latest evidence from trials exploring the benefits and risks of profound LDLc lowering the answer to the question 'How low do you go?' is, arguably, a straightforward '*As low as you can!*' There is, of course, the need for much longer follow up data for PCSK9 inhibitor trials, as is now available for statin studies (55). There are also measurement issues that are reviewed below since they impact on clinical practice (56), and cost-effectiveness concerns since PCSK9 inhibitors are expensive.

Figure 3 summarizes current thinking on the deployment of combination therapy to achieve lower LDLc levels. While guidelines advocate the use of high intensity statin treatment in high risk settings such as secondary prevention, it should be noted that the 'rule of 6%' applies in that doubling the statin dose will on average lower LDLc only by this amount (3,4,57); dose-response studies have shown consistently that each statin has a characteristic response at the starting dose e.g 37% LDLc lowering on 10mg of atorvastatin and that up-titration to a 20mg or 40mg dose produces a LDLc reduction of 43% and 48% respectively (57). This limitation on the action of statins is due, it is believed, to the counter-regulatory increase in PCSK9 induced by these drugs which has the effect of blunting the increase in LDL receptors and hence limiting LDLc reduction (58). International surveys reveal that while use of high intensity statin therapy is a recommended evidence-based approach, it is not sustained in regular clinical practice (59). Further, statins, though strongly recommended as first line therapy for lipid lowering have a well-characterised set of side-effects including increased propensity to develop diabetes especially in patients with pre-diabetes or known risk factors for

diabetes (3,4,33,38). Statin intolerance is also a recognised phenomenon and is often linked to myalgia and other muscle-related symptoms (33,60). These adverse reactions are dose dependent and can be a reason why 'high intensity' statin therapy recommended in the guidelines is not always used in practice. Combination therapy now tested in multiple clinical trials offers an effective alternative with potentially improved patient acceptance, and enhanced efficacy.

A number of reports have appeared on the health economics of combination lipid lowering therapy to achieve low or very low LDLc levels. There is general agreement that with the increased availability of generic ezetimibe, addition of this agent offers a cost-effective approach to lowering LDLc beyond what can be achieved with statins (61). Marketed PCSK9 inhibitors, however, cost about \$14,000 per year in the USA, and about €4,500 in Europe, and despite their considerable impact on LDLc are considered acceptable in terms of cost per quality-adjusted life year (QALY) only when there is a substantial discount, i.e. to a price of about \$9,000 per annum in the USA or less than £4,500 in the UK (62-65). In this context, the economics of CVD prevention is linked directly to the number of events prevented, the frequency of treatment-emergent side effects, as well as the price of the medication. To maximise event reduction and so minimise the cost per QALY, it is important to understand that the *absolute risk reduction* (number of events prevented over a given time) is considered by many commentators to be the key metric in deciding when profound LDLc lowering with combination therapy should be used (64-67). This parameter is estimated as the product of the patient's ongoing risk of a CVD event and the relative risk reduction attributable to further LDLc lowering. The latter is derived from the amount that LDLc is decreased in mg/dl using the 'rule of thumb' that for each 39mg/dl (1.0mmol/l) fall in LDLc there is 22% decrement in risk (9, 33,45). For example, both alirocumab and evolocumab consistently lower LDLc by 60 % on average (regardless of initial level). If the starting LDLc (on statin) is 130 mg/dl then this translates into a 78mg/dl (2.0mmol/l) drop which in turn provides a 44% decrease in CVD risk, and a potentially large absolute risk reduction. If, however, the starting LDLc is 75mg/dl then the relative risk reduction is

only about 25%, and the decrement in absolute risk proportionately less. (The commonly used term ‘*NNT*’ - the number-needed-to-treat - is the reciprocal of the absolute risk reduction and hence provides equivalent information (64)). Thus, NICE, the UK body which rules on the acceptability of new agents, mandated the use of PCSK9 inhibitors for those with high background risk – poly-vascular disease, multiple past CHD events – and elevated LDLc on maximum tolerated statin therapy (65). A similar approach has been recommended in updated guidance from the ACC Task Force (66) and the ESC/ EAS Task Force (67).

A strategy for profound LDLc lowering that takes into account the economic realities should therefore be based on risk stratification of the patient and an estimate of the benefit that would accompany the institution of combined lipid lowering treatment with a statin and ezetimibe first and then addition of a PCSK9 inhibitor (Figure 3) (66,67). Formal risk stratification schemes have been devised for acute coronary syndrome patients from data such as that from IMPROVE-IT (68) but more work is needed in this area to allow better targeting of therapy. In this setting, it is unlikely that primary prevention subjects with the exception of those with severe FH (64-67) will experience enough of an absolute reduction in CVD risk to justify adding a PCSK9 inhibitor to a statin/ezetimibe regimen.

Implications and implementation of profound LDL lowering paradigm.

Treatment targets: An important question that arises from recent trial results is ‘If a treatment goal for all secondary prevention/ high risk patients is to be used, should it now be set at a lower value?’ Targets for intervention are at best an artificial and idealised construct recommended by expert committees as a useful metric of therapeutic success (4,27). The monotonous relationship between LDL (or apoB-containing lipoproteins) and CVD risk that continues down to sub-physiological levels, and indeed virtually to zero (Figure 2) indicates that targets if they are employed are more a

reflection of 'willingness to intervene' rather than pathophysiologically derived landmarks.

International guidelines agree on the need for a >50% reduction in LDLc relative to off-treatment levels (3,4) and currently European and Canadian societies continue to recommend a target of <70mg/dl (4,27). Others have introduced <50mg/dl as a goal when risk is extremely high (69). This is a continuing topic of debate – should we have a more aggressive target that reflects the underlying pathology but creates a greater unmet need, or should we maintain <70mg/dl (in countries where it is recommended) and now ensure that the majority rather than a minority are able to reach this level with a combination of agents.

Measurement issues: There are a number of approaches to the laboratory assessment of LDLc concentration in the circulation. 'Beta-quantification' which uses centrifugation and precipitation to separate lipoprotein classes physically is the reference method. Direct LDLc tests, and the Friedewald calculation (based on knowing total plasma cholesterol and triglyceride and HDL cholesterol) are convenient, relatively inexpensive, and provide accurate measurements at normal and high levels (in the range 70 to 300 mg/dl). However, accuracy of the Friedewald equation falls off when triglyceride is elevated or LDLc is low (<70mg/dl) (56). Thus, for patients on combination lipid lowering treatment, the laboratory reported LDLc may be lower than the 'true' concentration (56). An alternative, more robust approach is to measure non-HDL cholesterol (total minus HDL) or apolipoprotein B levels that capture all atherogenic lipoproteins and these parameters are promoted in guidelines and expert opinion (4,27, 50,70). The apoB-containing lipoprotein species within 'non-HDL cholesterol' include, in addition to LDL, lipoprotein(a) and the cholesterol enriched 'remnants' of triglyceride-transporting chylomicrons and very low density lipoproteins. Recent evidence has linked both lipoprotein(a) (71) and remnants (72) to increased risk of cardiovascular disease. Assessment of non-HDL cholesterol or apoB when LDLc has been lowered profoundly with say a PCSK9 inhibitor may help reassure the patient that there is still a sufficiency of lipoproteins present

to perform the required metabolic transport tasks (the decrease in these variables is less than that seen for LDLc (12,34,35)), and may be a better marker of ongoing risk (70).

Patient prioritization: Profound LDLc lowering is most likely to be needed in patients with established disease, either those who have had an event, or those with advanced plaque present on imaging. As noted above, risk stratification in secondary prevention needs to be improved but at present those with stable disease could be managed with high intensity statin, or increasingly a combination of statin plus ezetimibe to achieve a 50% LDLc decrease and a level <70mg/dl. A 'highest risk-highest benefit' approach for patients with an aggressive disease course is a useful strategy for deciding when to add a PCSK9 inhibitor (64-67,73). In such patients, the high risk and elevated LDLc level on optimised statin therapy provides a substantial absolute risk reduction (low NNT) and satisfactory cost-effectiveness. The updated 2017 ESC/EAS guidelines set out thresholds of 140mg/dl for PCSK9 inhibitor initiation in patients with clinical atherosclerotic CVD and 100mg/dl in those severe, aggressive disease (67) (Figure 3). Once the decision has been made to add a PCSK9 inhibitor there is, according to the emerging paradigm, no target and neither is there a concern that the LDLc is too low. Data from trials indicate that the majority treated with this combination will have LDLc below 50mg/dl given the potency of the agents. In conclusion, in light of this emerging consensus on the most appropriate strategy for further LDLc lowering in very high risk patients, the pressing need now is to move to implementation.

References

1. Hovingh GK, Boekholdt SM, Stroes ES. Very low LDL-cholesterol concentrations achieved: which target is next? *Lancet*. 2017. pii: S0140-6736(17)32292-4. doi: 10.1016/S0140-6736(17)32292-4.
2. Sabatine MS, Giugliano RP. Low-Density Lipoprotein Cholesterol Treatment in the Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor Era: Getting Back on Target. *JAMA Cardiol*. 2017 Aug 2. doi: 10.1001/jamacardio.2017.2293.
3. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129: S1-45.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, De Backer G, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De Sutter J, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GY, Mach F, Mancía G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Ryden L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol*. 2016;23: Np1-np96.
5. Ioannidis JPA. Inconsistent Guideline Recommendations for Cardiovascular Prevention and the Debate About Zeroing in on and Zeroing LDL-C Levels With PCSK9 Inhibitors. *JAMA*. 2017;318:419-420.
6. Krumholz HM. Treatment of Cholesterol in 2017. *JAMA*. 2017;318:417-418.

7. Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. *JAMA*. 2015;314:142-150.
8. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial (letter). *JAMA* 2017;318:748-750.
9. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.
10. Redberg RF, Katz MH. Statins for primary prevention: The debate is intense but the data are weak. *JAMA* 2016;316:1979-81.
11. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387-2397.
12. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376:1713-1722.
13. Parhofer KG. New approaches to address dyslipidemia. *Curr Opin Lipidol*. 2017 doi: 10.1097/MOL.0000000000000456
14. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoğlu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459-2472

15. Kaplan H, Thompson RC, Trumble BC, Wann LS, Allam AH, Beheim B, Frohlich B, Sutherland ML, Sutherland JD, Stieglitz J, Rodriguez DE, Michalik DE, Rowan CJ, Lombardi GP, Bedi R, Garcia AR, Min JK, Narula J, Finch CE, Gurven M, Thomas GS. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet* (2017) [dx.doi.org/10.1016/S0140-6736\(17\)30752-3](https://doi.org/10.1016/S0140-6736(17)30752-3)
16. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264–1272
17. Raal FJ, Pilcher GJ, Waisberg R, Buthelezi EP, Veller MG, Joffe BI. Low-density lipoprotein cholesterol bulk is the pivotal determinant of atherosclerosis in familial hypercholesterolemia. *Am J Cardiol* 1999;83:1330-1333.
18. Rifkind BM, Segal P. Lipid Research Clinics Program reference values for hyperlipidemia and hypolipemia. *JAMA* 1983;250:1869-72.
19. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Aversa M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478-3490.
20. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr, Flack JM Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631-9
21. Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. *N Engl J Med*. 2016;375:2144-2153.
22. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet* 1994;344:1883-9.

23. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-07.
24. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495-504.
25. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352: 1425-35.
26. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J Jr, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2016;32:1263-1282
27. Shrank WH, Barlow JF, Brennan TA. New therapies in the treatment of high cholesterol: An argument to return to goal-based lipid guidelines. *JAMA* 2015;314:1443-4
28. Jarcho JA, Keaney JF. Proof that lower is better: LDL cholesterol and IMPROVE-IT. *N. Eng. J Med*. 2015;372:2448-50.
29. Giugliano RP, Wiviott SD, **Blazing** MA, De Ferrari GM, Park JG, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol: A Pre-specified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol*. 2017;2:547-555.
30. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016 doi: 10.1016/S0140-6736(16)31357-5.
31. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. Cognitive Function in a Randomized Trial of Evolocumab. *N Engl J Med*. 2017;377:633-643

32. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Gaciong ZA, Ceska R, Toth K, Gouni-Berthold I, Lopez-Miranda J, Schiele F, Mach F, Ott BR, Kanevsky E, Pineda AL, Somaratne R, Wasserman SM, Keech AC, Sever PS, Sabatine MS; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial *Lancet*. 2017 pii: S0140-6736(17)32290-0.
33. Preiss D, Sattar N. Pharmacotherapy: Statins and new-onset diabetes--the important questions. *Nat Rev Cardiol*. 2012;9:190-2.
34. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a pre-specified analysis of the FOURIER randomised controlled trial.. *Lancet Diabetes Endocrinol*. 2017 pii: S2213-8587(17)30313-3. doi: 10.1016/S2213-8587(17)30313-3.
35. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Aversa M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372:1489–1499.
36. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J* 2014;168:682–689.
37. Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. *Eur Heart J*. 2017 doi: 10.1093/eurheartj/ehx450
38. Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E, Landray MJ. Effects of Anacetrapib in Patients with

Atherosclerotic Vascular Disease. HPS3/TIMI55–REVEAL Collaborative Group, N Engl J Med. 2017;377:1217-1227

39. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlan E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kouz S, Tahirkheli N, Mason D, Nissen SE; Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. N Engl J Med. 2017;376:1933-1942
40. Davidson M, Liu SX, Barter P, Brinton EA, Cannon CP, Gotto AM Jr, Leary ET, Shah S, Stepanavage M, Mitchel Y, Dansky HM. Measurement of LDL-C after treatment with the CETP inhibitor anacetrapib. J Lipid Res. 2013;54:467-72.
41. Sniderman AD, Peterson ED Genetic Studies Help Clarify the Complexities of Lipid Biology and Treatment.. JAMA. 2017;318:915-917.
42. Ference BA, Kastelein JJP, Ginsberg HN, Chapman MJ, Nicholls SJ, Ray KK, Packard CJ, Laufs U, Brook RD, Oliver-Williams C, Butterworth AS, Danesh J, Smith GD, Catapano AL, Sabatine MS. Association of Genetic Variants Related to CETP Inhibitors and Statins With Lipoprotein Levels and Cardiovascular Risk. Ference BA, Kastelein JJP, Ginsberg HN, Chapman MJ, Nicholls SJ, Ray KK, Packard CJ, Laufs U, Brook RD, Oliver-Williams C, Butterworth AS, Danesh J, Smith GD, Catapano AL, Sabatine MS. JAMA. 2017;318:947-956
43. Shapiro MD. Rare Genetic Disorders Altering Lipoproteins. In: De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F, Vinik A, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-2015 Dec 6.
44. Packard CJ. Unpacking and Understanding the Impact of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Apolipoprotein B Metabolism. Circulation. 2017;135:363-365.
45. Packard C, Ford I. Long term follow up of lipid lowering trials. Curr. Opin. Lipidol. 2015;26:572-9.
46. Whelton SP, Meeusen JW, Donato LJ, Jaffe AS, Saenger A, Sokoll LJ, Blumenthal RS, Jones SR, Martin SS. Evaluating the atherogenic burden of individuals with a Friedewald-estimated

low-density lipoprotein cholesterol <70 mg/dL compared with a novel low-density lipoprotein estimation method. *J Clin Lipidol*. 2017;11:1065-1072.

47. Kotseva K, Wood D De Bacquer D et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Europ. J. of Preventative Cardiol*. 2015 DOI: 10.1177/2047487315569401.
48. Pokharel Y, Chinnakondapalli K, Vilain K, Wang K, Mark DB, Davies G, Blazing MA, Giugliano RP, Braunwald, E, Cannon CP, Cohen DJ, Magnusson EA. Impact of ezetimibe on the rate of cardiovascular-related hospitalizations and associated costs among patients with a recent acute coronary syndrome. *Circ. Cardiovasc. Qual. Outcomes*. 2017 ;10:e003201.DOI:10.1161/CIRCOUTCOMES.116.003201.
49. Sabatine MS. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: comparing and contrasting guidance across the Atlantic. *Eur Heart J*. 2017;https://doi.org/10.1093/eurheartj/ehw572.
50. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial (letter). *JAMA* 2017;318:748-750.
51. Robinson JG, Huijgen R, Ray K, Persons J, Kastelein JJ, Pencina MJ. Determining when to add nonstatin therapy: a quantitative approach. *J Am Coll Cardiol* 2016;68:2412-2421.
52. National Institute for Health and Care Excellence. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Technology appraisal guidance [TA393]. 2016. <https://www.nice.org.uk/guidance/ta393>.
53. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr. *J Am Coll Cardiol*. 2017;70:1785-1822.

54. Landmesser U, Chapman MJ, Stock JK, Amarenco A, Belch JJF, Boren J, Farnier MF, Ference BA, Gielen S, Graham I, Grobbee DE, Hovingh GK, Luscher TF, Piepoli MF, Ray KK, Stroes ES, Wiklund O, Windecker S, Zamorano JL, Pinto F, Tokgozoglu L, Bax JJ, and Catapano AL. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Europ. Heart J.* 2017; doi:10.1093/eurheartj/ehx549
55. Bohula EA, Morrow DA, Giugliano RP, Blazing MA, He P, Park JG, Murphy SA, White JA, Kesaniemi YA, Pedersen TR, Brady AJ, Mitchel Y, Cannon CP, Braunwald E. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol* 2017;69:911-921.
56. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists prevention of cardiovascular disease. *Endocr Pract.* 2017 ;23(Suppl 2):1-87.
57. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM Jr, Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;307:1302-1309.
58. Annemans L, Packard CJ, Briggs A, Ray KK. 'Highest risk-highest benefit' strategy: a pragmatic, cost-effective approach to targeting use of PCSK9 inhibitor therapies. *Europ Heart J.* 2018 (in press).
59. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med.* 2017;377:1119-1131.

Figure legends

Figure 1. Context and rationale for LDL lowering strategies.

The schematic depicts the change in LDL cholesterol over a life course in males (adapted from reference 19; for females, the rise in adulthood is largely delayed until the menopause). LDLc in familial hypercholesterolemia is elevated from birth and those with this condition have an enhanced integrated LDL exposure ('LDLc x years') and early atherosclerotic CVD (18). The risk reduction associated with a decrement in LDLc is predicted to be greater if an intervention to lower this lipoprotein is initiated earlier (21). It is speculated that this is due to the nature of the lesions present across the decades of life. The risk reductions relative to LDL lowering are extrapolated from reference 21.

Figure 2. Association of achieved LDLc with CVD risk in lipid lowering trials.

Figure 2A (adapted from reference 14) shows for trials of statin versus placebo, or more vs less intense statin treatment, achieved LDLc in the two arms of the study (linked by solid bar) and observed ongoing risk of a coronary event (fatal CHD plus non-fatal myocardial infarction). The vertical axes are adjusted to allow primary and secondary prevention studies to be examined together.

Figure 2B is taken from the FOURIER trial (reference 37 supplementary data). It shows for all subjects (i.e. in both treatment arms) grouped into 5 categories of increasing LDLc the relationship between mean achieved LDLc and event rate. The association is monotonous ($P < 0.001$ for trend) with no attenuation at even very low LDLc. The sub-group of lowest LDLc ($< 10 \text{ mg/dl}$) is also depicted; it had a commensurately low CVD risk.

Figure 3. Therapeutic strategies for profound LDL lowering.

This flowchart is illustrative of developing paradigms of combination lipid-lowering therapy (presented in much greater detail in references 66,67). It is envisaged that many patients with atherosclerotic vascular disease (ASCVD) will require up-titration of their statin dose to achieve guideline targets where these are recommended (e.g. in European/ Canadian guidelines 4, 27). There is a limit to what can be achieved with high intensity statin therapy. The need for further LDL lowering (and possibly patient preference) leads to routine addition of ezetimibe (51,66,67). Where there is a predicted very high CVD risk and an elevated LDLc then a PCSK9 inhibitor can be considered (64-67,73). Here the goal is to achieve a substantial absolute risk reduction (low NNT) personalized for the patient and acceptable to the payer. Annual risks (%/y) are quoted for illustrative purposes only; more detail on the type of CVD patient that will reach an appropriate risk threshold is given in references 64-67.

Figure 1

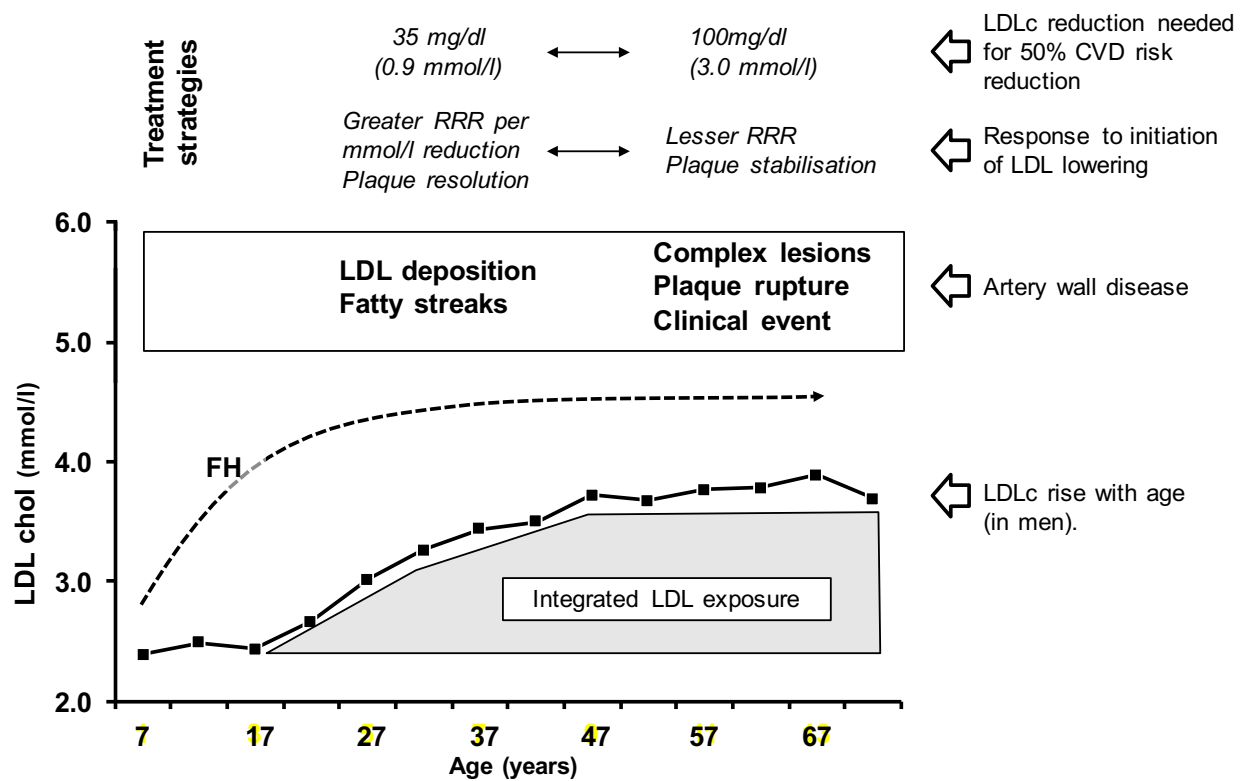
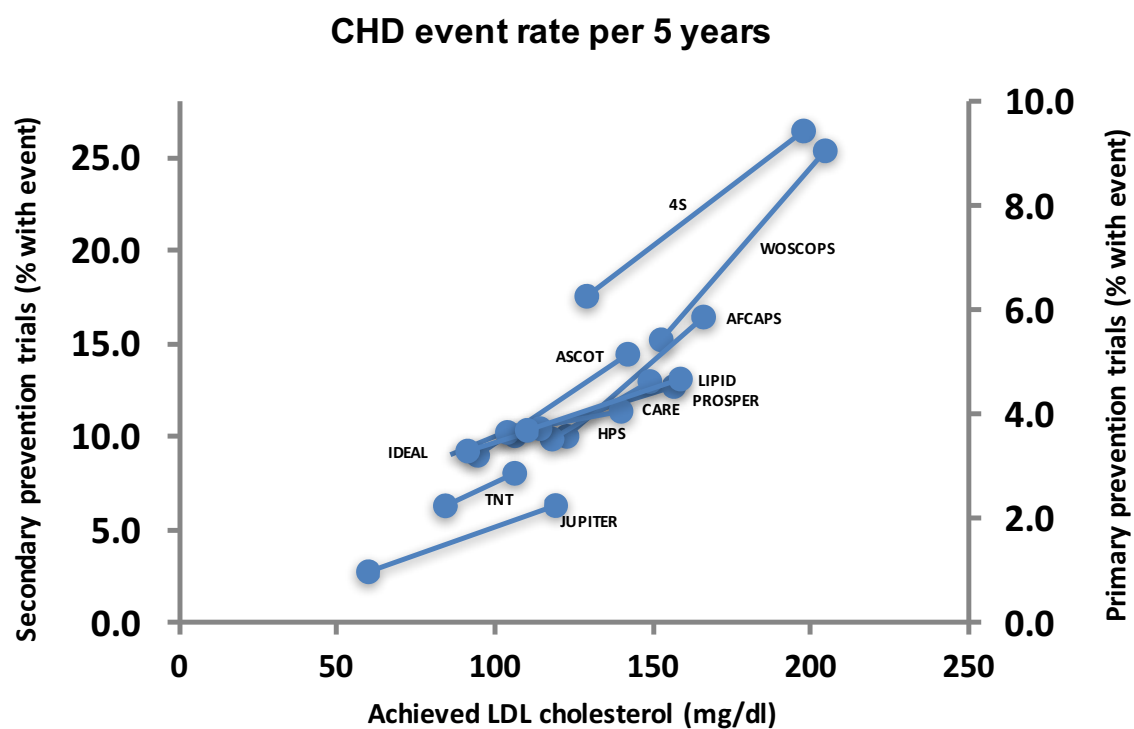


Figure 2

A



B

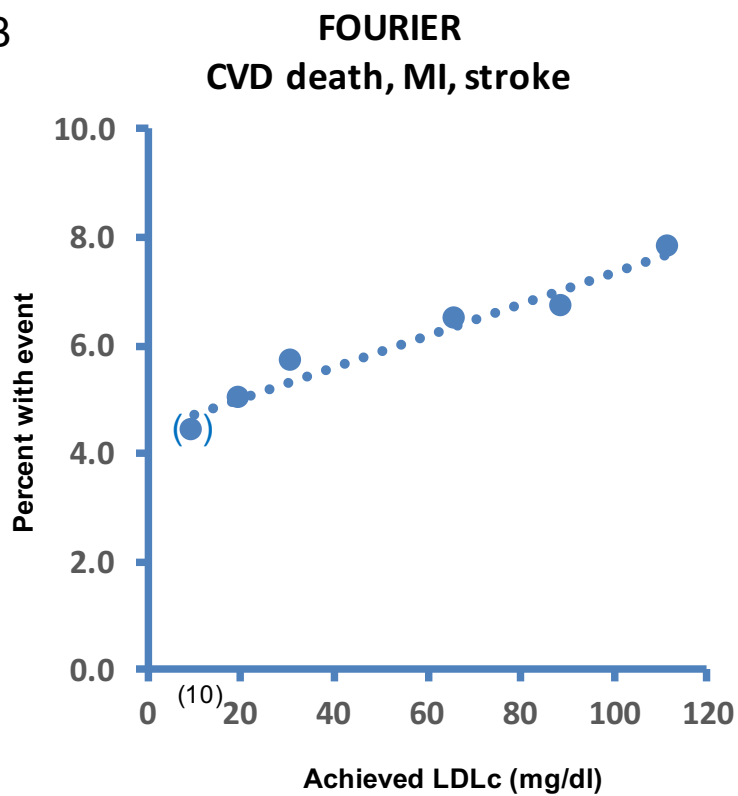


Figure 3

